REMARKS

These remarks are in response to the Office Action mailed January 2, 2004. Claims 1, 3, 6-9, 23, 28-29 and 31-32 have been amended. New claims 46 and 47 have been added. Support for the amendments and the new claims can be found throughout the specification as filed. No new matter is believed to have been introduced.

I. OBJECTIONS TO THE CLAIMS

Claims 1, 3, 4, 6, 7, 8, 23, 9, and 28-33 stand objected to for various informalities. Applicants have corrected these informalities as suggested by the Examiner. Applicants address the informalities of claim 3 and 28 (see, e.g., paragraph 6 of the Office Action), below. Accordingly, Applicants respectfully request withdrawal of the claim objections.

II. REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 1-8 and 23-28 stand rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse the rejection with respect to the pending claims.

Regarding paragraphs 13, 14 and 15 of the office action, the phrase "stably hybridizing portion" refers to the capturing oligonucleotides and the verification oligonucleotides (claims 1 and 23). The Examiner is referred to page 4, line 25 to page 5, line 15 of the specification, which explains what is meant by the phrase. Thus, in claims 3 and 28, the phrase refers to both the capturing and verification oligonucleotides. Accordingly, the phrase is clear and definite with reference to the specification and skill in the art.

With respect to paragraph 16, the Examiner is referred to page 7, lines 1-6 of the specification. In the embodiment claimed in claim 8, the signal amplifying agent (=second recognition agent) comprises a plurality of second recognition agents, e.g. a plurality of biotin molecules. One of the agents binds to the recognition partner, e.g. avidin, while the remaining unbound agents serve as first recognition agents to bind further recognition partners which in

turn may be bound by further second recognition agents. Thus, the newly added recognition partner does not bind to the original first recognition agent, but rather to the additional second recognition agents, which became first recognition agents.

Regarding paragraph 17 of the Office Action, Applicants believe that the term "microbalance quartz-crystal probe" in claim 26 is well known and understood by a person skilled in the art. For example, it may be an Au-quartz probe (see page 10, line 19). The Examiner is referred to page 2 of the specification, lines 16-21, and to the reference cited there (no. 11, Bardea, et al.), and also to page 6, lines 1-5, and to WO 97/04314 cited there, especially page 4, lines 19-24. Accordingly, there can be no doubt based upon the information available in the art that "microbalance quartz-crystal probe" are well known and thus are not indefinite.

For at least the foregoing reasons, the rejections under 35 U.S.C. §112, second paragraph should be withdrawn.

III. REJECTION UNDER 35 U.S.C. §102

Claims 1 and 2 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Meade et al. (U.S. Patent No. 5,591,578). Applicants respectfully traverse with respect to the pending claims.

In order to distinguish the prior art, it is necessary to correctly understand Applicants' claimed invention. The method of the invention is a method for detecting a target oligonucleotide in a sample using an immobilized capture oligonucleotide and a free verification oligonucleotide. The method employs two independent binding events to increase specificity and signal amplification thereby increasing sensitivity. The measurement of the signal as defined in amended claim 1 and new claim 45 may be performed in one or both of the following two ways: (1) by measuring insulation or resistance of the sensing interface to interfacial electron transfer between the sensing interface and the surrounding medium (supported on page 5, lines 19-28 and page 14, lines 3-12); (2) by measuring an increase in the mass immobilized on the sensing interface (supported on page 7, lines 7-28). None of the cited references, nor their combination, disclose the method of the invention as defined above.

Meade et al. disclose selective modification of nucleic acids at specific sites with redox-active moieties (col. 5, lines 31-33). These redox-active moieties comprise an electron donor and an electron acceptor (col. 5, lines 43-45). Meade et al. also disclose a method of detecting a target sequence by measuring an electron transfer rate between the electron donor and the electron acceptor (col. 6, lines 60-67). In order to detect the target sequence according to Meade et al., the introduction of a redox-active component into the DNA complex generated on the electrode is mandatory. The incorporated redox-active component signals the hybridization event by electron exchange between the redox-active component and the electrode (col. 17, lines 9-15). The essence of the method of Meade et al. is the formation of conditions for electron exchange.

In contrast, in Applicants' claimed invention a nucleic acid-bound redox-active label is excluded for the hybridization event. A redox-active component is not incorporated into the hybridization complex, but is rather in solution. Furthermore, the invention does not aim to generate electron exchange between a redox label and the electrode to measure hybridization. On the contrary, in the method of the invention (as defined in claim 1), electron transfer through the interface is blocked, and the blocking (insulating/resistance) effect is used to follow the hybridization.

While Meade et al. monitor electron transfer properties between molecule labels introduced into the hybridization complex, a method of the invention (as set forth in claim 46) follows an increase in the mass immobilized on the interface as a result of hybridization, e.g. precipitation of an insoluble product (claim 9) or binding of a liposome (claim 23). While the Meade et al. approach requires generation of electron transfer to follow hybridization; a method of the invention involves a change in the interfacial properties of the sensing interface so that the electron transfer is blocked.

Thus, Meade et al. do not teach or suggest each and every element of Applicants' claimed invention (e.g., part (e) of claim 1, "detecting the presence of said verification oligonucleotides on the sensing interface by measuring insulation of the sensing interface to interfacial electron transfer between the sensing interface and the surrounding medium"). Accordingly, Applicants respectfully request withdrawal of the §102(b) rejection.

Claims 1-3, 6, 23-26 and 28 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by Durst et al. (U.S. Patent No. 6,359,752). Applicants respectfully traverse with respect to the pending claims.

Durst et al. disclose a method for measuring an analyte in a test sample which employs two binding materials, one conjugated to marker-encapsulating liposomes and the other immobilized on a portion of an absorbent material (col. 6, lines 28-31). When the analyte is a nucleic acid sequence, the binding materials are probes preferably between 17 and 25 nucleotides long (col. 7, lines 18-28). The electroactive marker released from the liposome undergoes redox cycling in an interdigitated electrode array (col. 4, lines 1-43). With reference to Fig. 6 and the corresponding description in col. 12, lines 4-23, the absorbent material 510 to which the capture probe 514 is bound, is a different entity from the electrode array 512. The electrochemical probe in Durst et al. is the interdigitated electrode. In Durst et al., the entire sensor configuration is not assembled on the electrochemical probe of the device. The hybridization and lysis of the liposomes occur on a second absorbent material that is not an electrochemical probe.

In contrast, in Applicants' claimed invention the capturing oligonucleotides are carried on the sensing interface. The Examiner should note that if Durst et al. would place the capturing nucleic acid and the resulting hybridization complex directly on the interdigitated electrode, the redox cycling which is used to measure the analyte would be blocked. Therefore Durst et al. require 2 separate components. Applicants' invention, on the other hand, measures the changes in electron transfer resistance of the electrode. Furthermore, Applicants' methods measure electrostatic repulsion of the oxidized form of the redox label, and not the electrical response of the redox marker released from the liposomes. Durst et al. do not monitor direct changes in the interfacial properties of the surface as a result of hybridization as in the method of the invention.

With respect to claims 3 and 28, Durst et al. teach probes which are between 17 and 25 nucleotides long, while claims 3 and 28 teach oligonucleotides of about 12 nucleotides.

For at least the foregoing reasons, Durst et al. cannot anticipate Applicants' claimed invention. Accordingly, Applicants respectfully request withdrawal of the §102(e) rejection.

IV. REJECTION UNDER 35 U.S.C. §103

Claims 4, 5 and 7 stand rejected under 35 U.S.C. §103 as allegedly unpatentable over Durst et al., as applied to claims 1-3, 6, 23-26 and 28 above, and further in view of Lemar et al. (U.S. Patent No. 6,096,508). Applicants respectfully traverse this rejection with respect to the pending claims.

Durst et al. was addressed above. Lemar teaches a method for reducing background signal problems in detection methods involving biotinylated molecules. Lemar does not disclose the binding of oligonucleotides to a sensing interface, and therefore does not remedy the deficiencies of Durst et al. The examiner should note that the surface coverage of the double-stranded DNA on the electrode surface (or the Quartz crystal) is very small. As a result, the amount of bound avidin to the surface is very low. It is not obvious that this small amount of bound avidin will change the interfacial properties of the surface. Applicants' patent application demonstrates that indeed impedance spectroscopy provides a useful method to follow these minute changes in the interface properties enabling the detection of DNA hybridization.

Claim 27 stands rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Durst et al., as applied to claims 1-3, 6, 23-26 and 28 above, and further in view of Okahata et al. (Anal. Chem. 70:1288-1298, 1998). Applicants respectfully traverse with respect to the pending claims.

Durst et al. was discussed above. Okahata et al. teach measurement of DNA hybridization on an oligonucleotide-immobilized 27-MHz quartz crystal microbalance. Okahata does not disclose measuring electrostatic repulsion of the oxidized form of the redox label, nor monitoring direct changes in the interfacial properties of the surface as a result of hybridization as in the method of Applicants' invention and therefore does not remedy the deficiencies of Durst et al.

Thus, Applicants submit that the combination of Durst et al. with either of Lemar et al. or Okahata et al. do not remedy the deficiencies of the primary reference and do not render Applicants' invention obvious. Accordingly, Applicants respectfully request withdrawal of the §103 rejections.

Enclosed is a $61 check for excess claim fees. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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